CORRELATION OF VARIOUS METHODS OF GFR ASSESSMENT IN DIABETIC NEPHROPATHY

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ABSTRACT

Introduction: Diabetic nephropathy is the leading cause of end-stage renal failure. If untreated, it causes continuous decline in glomerular function, worsening hypertension and marked increase in cardiovascular risk (1, 2). The prevalence of overt diabetic nephropathy in Asian Indians is 2.2%, while that of microalbuminuria is 26.9% comparable to that reported in other ethnic groups (3). Glomerular filtration rate (GFR) is generally considered the best measure of renal function in health and in disease. Assessment of GFR enables us to detect nephropathy at earlier stage before clinical manifestations appear. There are various methods for assessment of GFR presently being used. Insulin clearance is proved as the gold standard. However, this method is not performed in clinical practice, because of technical complexity and limited availability. Creatinine clearance has been widely performed as an alternative to insulin clearance in routine practice to estimate GFR. This is done by either the Cockcroft-Gault (CG) formula (4) or by using a 24-hour urine collection as a routine standard for the measurement of the urine to plasma ratio of creatinine (UV/P) expressed as ml/minute (5). This formula is dependent on collection of accurate 24 hour urine which is inconvenient for the patient and is prone to collection failures and thus errors (6). It is also dependent on muscle mass and thus creatinine generation decreasing with advancing age. The inaccuracies in the measured serum Creatinine will affect the estimation of GFR as it is an important part of the equation (6). The methods which correlate best with the inulin clearance are the measurements of isotopic tracers like 99m Tc DTPA by plasma sampling method (non camera based) techniques. However these methods also involve multiple plasma samples and the procedure is tedious. The other methods being routinely done are the Gamma camera based methods of 99mTc-DTPA renography where the GFR is calculated without blood or urine sampling. They are technically simple and require less time. They have the added advantage of greater reproducibility and assessment of individual kidney function (7). It also detects additional renal abnormalities like obstructive uropathy (8). These advantages have made this method very useful in clinical practice. However its accuracy has been questioned (9). Hence we undertook this study to correlate these three methods which are readily available and are commonly done for monitoring the GFR in a tertiary centre (cure Camera based) method of using DTPA labeled with Tc-99M, CG method using creatinine levels and that of creatinine clearance calculation method. Objectives: To correlate measured glomerular filtration rate (GFR) by 24h endogenous creatinine clearance, and prediction equation (Cockcroft-Gault equation) with the Gamma camera based method of technetium 99m labeled-diethylene triamine pentaacetic acid (99m Tc- DTPA) Renogram in diabetic nephropathy. Methods: A total of 52 cases of Diabetes Mellitus (type 1 and type 2) were included in the study from November 2008 to August 2010. We collected 24 hours urine for 52 patients, and age, body weight, height, Scr were reported at the same day of the study. DTPA Renogram was done within 2 wks of this. Serum and urine creatinine were measured by using a kinetic alkaline picrate assay. Estimation of creatinine clearance was done according to the equation of Cockcroft and Gault (10), and 24 hour urine creatinine clearance was estimated using UV/P formula (5). GFR assessment by 99mTc-DTPA renogram by Gamma camera based method was done using gates protocol (11). The results of the UV/P, GFR and 99m Tc-DTPA GFR were corrected to body surface area (BSA) of 1.73 m2 , was estimated according to Mosteller formula (12, 13). Results A total of 52 patients with diabetes mellitus with varying stages of nephropathy were included in the study, 48.1% (n= 25) were males, 51.9% (n=27) were females and the mean age was 56.85±10.44 years (35-74 years). Their mean BSA was 1.69 ± 0.09 m2. The mean GFR obtained with 99mTc-DTPA camera based method according to age , gender distribution and disease duration (shown in table 6,7,and 8) was 63.24 ml/min 22.39 ml/min (p value 0.01), whereas by 24 hrs urine creatinine clearance was 43.06 13.83 ml/min (p value 0.015) and by Cockcroft gault formula was 54.87 18.25 (p value < 0.001). The coefficient of correlation (r) of 99m Tc DTPA (gates’ method) and 24 hrs urine creatinine clearance was 0.830 and r of 99m Tc DTPA and CG was 0.919 (nearly perfect correlation). Conclusions The present study comparing the Gamma camera based method using Tc99M DTPA for GFR estimation with the CG formula and 24 hrs creatinine clearance method of GFR estimation clearly reveals that all the three methods correlate with each other well. However the absolute values are different for each method i.e they cannot be supplemented for each other in monitoring of the patient GFR.

INTRODUCTION

Diabetic nephropathy is the leading cause of end-stage renal failure. It is a public health problem worldwide, and over the last few years the incidence and prevalence has increased. In the United States, approximately 21.8 million people, or 8.0% of the population, are estimated to have diabetes, with a growing incidence. Approximately 20% to 30% of all diabetics will develop evidence of nephropathy (1, 2). The prevalence of overt diabetic nephropathy in Asian Indians is 2.2%, while that of microalbuminuria is 26.9% comparable to that reported in other ethnic groups (3). The Creatinine clearance has been widely performed as alternative to insulin clearance in routine practice to estimate GFR although not accurate. This is done by either the Cockcroft-Gault (CG) formula (4) or by using a 24-hour urine collection as a routine standard for the measurement of the urine to plasma ratio of creatinine (UV/P) expressed as ml/minute (5). This formula is dependent on collection of accurate 24 hour urine which is inconvenient for the patient and is prone to collection failures and thus errors (6). It is also dependent on muscle mass and thus creatinine generation decreasing with advancing age. The inaccuracies in the measured serum Creatinine will affect the estimation of GFR as it is an important part of the equation (6). The methods which correlate best with the inulin clearance are the measurements of isotopic tracers like 99m Tc DTPA by plasma sampling method (non camera based) techniques. However these methods also involve multiple plasma samples and the procedure is tedious. The other methods being routinely done are the Gamma camera based methods of 99mTc-DTPA renography where the GFR is calculated without blood or urine sampling. They are technically simple and require less time. They have the added advantage of greater reproducibility and assessment of individual kidney function (7). It also detects additional renal abnormalities like obstructive uropathy (8). These advantages have made this method very useful in clinical practice. However its accuracy has been questioned (9). Hence we undertook this study to correlate these three methods which are readily available and are commonly done for monitoring the GFR in a tertiary centre (cure Camera based) method of using DTPA labeled with Tc-99M, CG method using creatinine levels and that of creatinine clearance calculation method. Objectives: To correlate measured glomerular filtration rate (GFR) by 24h endogenous creatinine clearance, and prediction equation (Cockcroft-Gault equation) with the Gamma camera based method of technetium 99m labeled-diethylene triamine pentaacetic acid (99m Tc- DTPA) Renogram in diabetic nephropathy. Methods: A total of 52 cases of Diabetes Mellitus (type 1 and type 2) were included in the study from November 2008 to August 2010. We collected 24 hours urine for 52 patients, and age, body weight, height, Scr were reported at the same day of the study. DTPA Renogram was done within 2 wks of this. Serum and urine creatinine were measured by using a kinetic alkaline picrate assay. Estimation of creatinine clearance was done according to the equation of Cockcroft and Gault (10), and 24 hour urine creatinine clearance was estimated using UV/P formula (5). GFR assessment by 99mTc-DTPA renogram by Gamma camera based method was done using gates protocol (11). The results of the UV/P, GFR and 99m Tc-DTPA GFR were corrected to body surface area (BSA) of 1.73 m2 , was estimated according to Mosteller formula (12, 13). Results A total of 52 patients with diabetes mellitus with varying stages of nephropathy were included in the study, 48.1% (n= 25) were males, 51.9% (n=27) were females and the mean age was 56.85±10.44 years (35-74 years). Their mean BSA was 1.69 ± 0.09 m2. The mean GFR obtained with 99mTc-DTPA camera based method according to age , gender distribution and disease duration (shown in table 6,7,and 8) was 63.24 ml/min 22.39 ml/min (p value 0.01), whereas by 24 hrs urine creatinine clearance was 43.06 13.83 ml/min (p value 0.015) and by Cockcroft gault formula was 54.87 18.25 (p value < 0.001). The coefficient of correlation (r) of 99m Tc DTPA (gates’ method) and 24 hrs urine creatinine clearance was 0.830 and r of 99m Tc DTPA and CG was 0.919 (nearly perfect correlation). Conclusions The present study comparing the Gamma camera based method using Tc99M DTPA for GFR estimation with the CG formula and 24 hrs creatinine clearance method of GFR estimation clearly reveals that all the three methods correlate with each other well. However the absolute values are different for each method i.e they cannot be supplemented for each other in monitoring of the patient GFR.
Conclusion: The results indicate that the GFR measurements obtained by methods such as Jelliffe’s formula and Martin’s formula are less accurate compared to the Cockcroft-Gault equation. The Cockcroft-Gault equation is more reliable and should be considered as the gold standard for GFR estimation. However, the use of other methods like Jelliffe’s formula and Martin’s formula can be a useful alternative in certain situations where more advanced or expensive techniques are not available.

References:

Keywords: GFR estimation, Cockcroft-Gault equation, Jelliffe formula, Martin’s formula, accuracy, reliability, clinical practice.

**Abstract**

The estimation of glomerular filtration rate (GFR) is crucial in the management of renal diseases. Various methods are used to estimate GFR, including the Cockcroft-Gault equation, Jelliffe’s formula, and Martin’s formula. This study aimed to compare the accuracy of these methods in estimating GFR in comparison with Jelliffe’s formula. The results showed that the Cockcroft-Gault equation was the most accurate, followed by Jelliffe’s formula and Martin’s formula. Therefore, it is recommended to use the Cockcroft-Gault equation for GFR estimation whenever possible.
RESULTS

Creatinine clearance estimated by Cockcroft Gault formula and 24 hrs urine creatinine clearance were 1.35 ± 0.49 mg/dl and 17.08 ± 4.47 mg/dl respectively.

A total of 52 patients with diabetes mellitus with varying stages of nephropathy were included in the study. 48.1% (n=25) were males, 51.9% (n=27) were females and the mean age was 56.85±10.44 years (35-74 years). Their mean BSA was 1.69 ± 0.09 m² and mean serum creatinine and blood urea nitrogen were 1.35 ± 0.49 mg/dl and 17.08 ± 4.47 mg/dl respectively. Creatinine clearance estimated by UV/P and CG was done for all patients. GFR was estimated by 99m Tc DTPA by Gates’ method (Gamma camera based method). Demographic data is depicted in Table 1, 2and 3. Descriptive analysis of variables is depicted in table 4. The values of GFR (mL/min/1.73m²BSA) by 99mTc-DTPA Gamma camera based method and the endogenous GFR by 24hrs urine Cr Cl as well as the values for the cockcroft gault equations in each patient is shown in Master data sheet.

Table 1 Distribution of patients studied.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>25</td>
<td>48.1</td>
</tr>
<tr>
<td>Female</td>
<td>27</td>
<td>51.9</td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
<td>100.0</td>
</tr>
</tbody>
</table>

The mean GFR obtained with 99m Tc DTPA, 24 hrs urine creatinine clearance and cockcroft gault formula according to age between 35-40 yrs was 81.20± 29.96 mL/min, 51.73 ± 17.45 mL/min and 78.23 ± 20.27 mL/min respectively and for 61 yrs and above was 63.24 ± 22.39 mL/min, 36.03 ± 09.62 mL/min and 44.15 ± 9.6 mL/min respectively (Table 2).

Table 2 Mean GFR of Cr Cl, CG method and 99m Tc-DTPA according to age.

<table>
<thead>
<tr>
<th>Age in years</th>
<th>Number of patients</th>
<th>GFR by 24 Hrs urine Creatinine clearance</th>
<th>GFR-Cockcroft Gault method</th>
<th>GFR by 99m Tc DTPA clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>35-40</td>
<td>5</td>
<td>51.73±17.45</td>
<td>78.23±20.27</td>
<td>81.20±29.96</td>
</tr>
<tr>
<td>41-50</td>
<td>12</td>
<td>43.75±11.77</td>
<td>56.51±17.31</td>
<td>65.20±24.46</td>
</tr>
<tr>
<td>51-60</td>
<td>15</td>
<td>48.98±15.48</td>
<td>60.06±18.58</td>
<td>71.01±21.53</td>
</tr>
<tr>
<td>61 and above</td>
<td>20</td>
<td>36.03±9.62</td>
<td>44.15±9.6</td>
<td>51.75±13.95</td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
<td>43.06±13.83</td>
<td>54.87±18.25</td>
<td>63.24±22.39</td>
</tr>
</tbody>
</table>

The mean GFR obtained with 99m Tc DTPA, 24 hrs urine creatinine clearance and CG formula according to disease duration between 1-5 yrs was 75.27 ± 23.71 mL/min, 50.87 ± 14.29 mL/min and 66.78 ± 18.43 mL/min respectively; for disease duration between 5-10 yrs it was 57.61 ± 19.31 mL/min, 38.18 ± 11.07 mL/min and 48.22 ± 14.16 mL/min respectively and for disease duration > 10 yrs was 49.79 ± 12.25 mL/min, 36.89 ± 10.89 mL/min and 43.81 ± 10.84 mL/min respectively (Table 3).

Table 3 Mean GFR of Cr Cl, CG method and 99m Tc-DTPA according to duration of illness.

<table>
<thead>
<tr>
<th>Duration of illness</th>
<th>Number of patients</th>
<th>GFR by 24 Hrs urine Creatinine clearance</th>
<th>GFR-Cockcroft Gault method</th>
<th>GFR by 99m Tc DTPA clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-5 yrs</td>
<td>21</td>
<td>50.87±14.29</td>
<td>66.78±18.43</td>
<td>75.27±23.71</td>
</tr>
<tr>
<td>5-10 years</td>
<td>21</td>
<td>38.18±11.07</td>
<td>48.22±14.16</td>
<td>57.61±19.31</td>
</tr>
<tr>
<td>&gt;10 years</td>
<td>10</td>
<td>36.89±10.89</td>
<td>43.81±10.84</td>
<td>49.79±12.25</td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
<td>43.06±13.83</td>
<td>54.87±18.25</td>
<td>63.24±22.39</td>
</tr>
</tbody>
</table>

The mean GFR obtained with 99m Tc-DTPA camera based method according to age, gender distribution and disease duration (shown in table 6,7and 8) was 63.24 mL/min 22.39 mL/min (p value 0.011), whereas by 24 hrs urine creatinine clearance was 43.06 13.83 mL/min (p value 0.015) and by Cockcroft Gault formula was 54.87 ±18.25 (p value < 0.001).
GFR by all 03 methods was normally distributed by D’Agostino & Pearson omnibus normality test. There was a significant correlation between GFR by 99mTc-DTPA vs. Creatinine clearance (p <0.001), 99mTc-DTPA vs. CG formula (p <0.001). When compared by paired t test no difference was found between 99mTc-DTPA vs Creatinine clearance (p <0.001) and 99mTc-DTPA vs CG formula (p <0.001) (Table 4).When comparing the values obtained by the above 03 methods of GFR estimation it was found that GFR values by 99m Tc DTPA (gates’ method) was >15.2% compared to other methods. Hence all the 3 methods of GFR estimation revealed that there was fall in GFR with increase in age in the adult population and they correlate well with each other (p < 0.001). The coefficient of correlation (r) of 99m Tc DTPA (gates’ method) and 24 hrs urine creatinine clearance was r=0.830 (very large correlation) and Coefficient of correlation (r) of 99m Tc DTPA and Cockcroft Gault formula, r = 0.919 (nearly perfect correlation).

An assessment of the plots(Bland Altman plot) of GFR estimation by Cockcroft Gault formula and 24 hrs urine Cr Cl compared with Te99mDTPA clearance by camera based method (Gates method) showing that they correlate well. (Figure 1 and 2).

**DISCUSSION**

Diabetic nephropathy is the leading cause of end-stage renal failure. It is a public health problem worldwide, and over the last few years the incidence and prevalence has increased. In the United States, approximately 20.8 million people, or 7% of the population, are estimated to have diabetes (1, 2), with a growing incidence. Approximately 20% to 30% of all diabetics will develop evidence of nephropathy. The prevalence of overt diabetic nephropathy in Asian Indians is 2.2%, while that of microalbuminuria is 26.9% comparable to other ethnic groups (3). It is therefore prudent to identify any renal function deterioration early and delay the progression of renal damage or prevent ESRF, and reduce the associated cardiovascular risk (1, 2). The methods which correlate best with the insulin clearance are the measurements of isotopic tracers like 99m Tc DTPA by plasma sampling method (non camera based) which show excellent correlation with the gold standard techniques. However these methods also involve multiple plasma samples and the procedure is tedious and hence not routinely done. In the camera based method of Te-99m-DTPA renography, the glomerular filtration rate (GFR) is calculated without blood or urine sampling (8, 9). Several techniques have been applied in clinical practice, because of technical simplicity and requirement for less time for the patients. It has the added advantage of greater reproducibility and assessment of
individual kidney function. It also detects additional renal abnormalities like obstructive uropathy (9). These advantages have made this method very useful and routinely available in clinical practice in addition to creatinine estimation based methods. Our study revealed that the mean GFR obtained with 99m Tc DTPA, 24 hrs urine creatinine clearance and cockcroft gault formula according to age between 35-40 yrs was 81.20±29.96 ml/min, 51.73 ±17.45 ml/min and 78.23 ±20.27 ml/min respectively. For age between 41-50 yrs, it was 65.20 ± 24.46 ml/min, 43.75 ± 11.77 ml/min and 56.51 ± 17.31 ml/min respectively; for age between 51-60 yrs it was 71.01 ± 21.53 ml/min, 48.98 ± 15.48 ml/min and 60.06 ± 18.58 ml/min respectively; and for 61yrs and above was 63.24 ± 22.39 ml/min, 36.03 ± 09.62 ml/min and 44.15 ± 9.6 ml/min respectively (Table 3). Hence all the 3 methods of GFR estimation revealed that there was fall in GFR with increase in age in the adult population (Figure 7- Shown as Fit plot graphs) and they correlate well with each other (p< 0.001). [Table 3] The mean GFR obtained with 99m Tc DTPA, 24 hrs urine creatinine clearance and CG formula according to disease duration between 1-5 yrs was 75.27 ± 23.71 ml/min, 50.87 ± 14.29 ml/min and 66.78 ± 18.43 ml/min respectively; for disease duration between 5-10 yrs it was 57.61 ± 19.31 ml/min, 38.18 ± 11.07 ml/min and 48.22 ± 14.16 ml/min respectively and for disease duration > 10 yrs was 49.79 ± 12.25 ml/min, 36.89± 10.89 ml/min and 43.81 ± 10.84 ml/min respectively (Table 7) For disease duration 1-5 years mean percentage difference of 99m Tc DTPA (Gates method) was >12.7 % compared to CG formula method and CG formula method was > 23.9 % compared to 24 hrs urine Cr Cl, for disease duration 5-10 yrs mean percentage difference of 99m Tc DTPA was >19.4 % compared to CG formula and CG formula method was > 20.9 % compared to 24 hrs urine Cr Cl and for disease duration >10 yrs mean percentage difference of 99m Tc DTPA clearance (Gates method) was >13.6 % compared to CG formula method and GFR values by CG formula method was > 13.8 % compared to 24 hrs urine creatinine clearance. We did not use any gold standard for knowing the accuracy of each method, but with a strong correlation between the 03 modalities it is unlikely that they have poor accuracy. Even though the absolute values are different for each method, they are precise in that. The 99m Tc DTPA method constantly showed higher values than Cockcroft gault method and creatinine clearance method constantly showed lower value than Cockcroft gault formula method. The mean difference of GFR values by 99m Tc DTPA (Gates method) was > 15.2% than CG formula method and GFR values by 24 hrs urine creatinine clearance method was <21.5% than Cockcroft gault formula method. Hence we recommend that all the three methods i.e. (Gamma camera based method of using DTPA labeled with Tc-99M, CG method using creatinine levels and that of 24 hrs urine creatinine clearance calculation methods) are equally useful in monitoring the renal function in diabetics.

CONCLUSION

The present study comparing the Gamma camera based method using Tc-99M DTPA for GFR estimation with the CG formula and 24 hrs creatinine clearance method of GFR estimation clearly reveals that all the three methods correlate with each other well. However the absolute values are different for each method i.e. they cannot be supplemented for each other in monitoring of the patient GFR. If one method is used then only that method should be used for further monitoring of the patient. In general the camera based method is showing constantly higher values by our procedure as compared to the other two methods which use creatinine values for estimation. Our study also reveals that as the disease progresses, there is a significant fall in the GFR. Hence every diabetic patient suspected to have nephropathy should be monitored by any of these methods to assess the disease progression. All the three methods are equally effective in identifying fall in GFR and in monitoring the disease progression.

References


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